CHROMIUM EFFECTS ON GLUCOSE TOLERANCE AND INSULIN SESITIVITY IN PERSONS AT RISK FOR DIABETES MELLITUS

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Abstract

Objective—To investigate the effects of daily chromium picolinate supplementation on serum measures of glucose tolerance and insulin sensitivity in patients at high risk for type 2 diabetes mellitus.

Methods—We conducted a randomized, double-blind, placebo-controlled, modified cross-over clinical trial with 6-month sequences of intervention and placebo followed by a 6-month postintervention assessment. Adult patients with impaired fasting glucose, impaired glucose tolerance, or metabolic syndrome were enrolled. Participants received 6-month sequences of chromium picolinate or placebo at 1 of 2 dosages (500 or 1000 mcg daily). Primary outcome measures were change in fasting plasma glucose, 2-hour plasma glucose during oral glucose tolerance testing, fasting and 2-hour insulin, and homeostasis model assessment of insulin resistance (HOMA-IR). Secondary outcomes included anthropometric measures, blood pressure, endothelial function, hemoglobin A_{1c}, lipids, and urinary microalbumin.

Results—Fifty-nine participants were enrolled. No changes were seen in glucose level, insulin level, or HOMA-IR (all, $P > .05$) after 6 months of chromium at either dosage level (500 mcg or 1000 mcg daily) when compared with placebo. None of the secondary outcomes improved with either chromium dosage compared with placebo ($P > .05$).

Conclusions—Chromium supplementation does not appear to ameliorate insulin resistance or impaired glucose metabolism in patients at risk for type 2 diabetes and thus is unlikely to attenuate diabetes risk.

INTRODUCTION

Impaired glucose tolerance (IGT), impaired fasting glucose (IFG), and metabolic syndrome are considered precursors to type 2 diabetes mellitus (1). Endothelial dysfunction is also associated with increased risk for diabetes and is directly linked to insulin resistance (2) and hyperglycemia.

Although pharmacotherapy with such drugs as metformin, acarbose, orlistat, and thiazolidinediones can reduce risk of type 2 diabetes (3), their cost and potential adverse effects can be objectionable to patients who do not yet have an actual disease (4). Intensive diet and lifestyle change can have an important role in diabetes prevention (5), although adherence to these regimens is often difficult (6).

The micronutrient chromium is of interest in this regard as a potential means of improving glucose tolerance (7,8) by reducing insulin resistance (9). Chromium picolinate is widely marketed to the public with diverse health claims pertaining to glucose metabolism, insulin action, muscle mass, weight control, and diabetes prevention (10). In 2002, estimated sales of chromium-based supplements was $85 million (11). Indeed, one of the more common nutrition-related questions posed by patients with or at risk for diabetes to practicing endocrinologists concerns the effectiveness of chromium.

To assess the efficacy of this popular nutritional supplement, we performed a randomized controlled trial designed to investigate the effects of daily chromium picolinate supplementation for 6 months at 2 dosage levels on serum measures of glucose tolerance and insulin sensitivity. Because of the association of derangements in these metabolic abnormalities with endothelial dysfunction, brachial artery reactivity was also assessed before and after therapy.

RESEARCH DESIGN AND METHODS

Participants

Patients enrolled were 18 years or older and were identified as having IGT, IFG, or metabolic syndrome.

IGT was diagnosed by American Diabetes Association guidelines (1), which require the following 2 criteria: (a) a plasma glucose concentration 2 hours after consuming 75 g of glucose of at least 140 mg/dL, but below 200 mg/dL, and (b) a fasting plasma glucose (FPG) concentration less than 126 mg/dL.

IFG was diagnosed using the American Diabetes Association criteria of a FPG concentration of 100 mg/dL or greater, but less than 126 mg/dL (1).

Metabolic syndrome was diagnosed using National Cholesterol Education Panel Adult Treatment Panel III criteria (12), requiring the presence of 3 of the following 5 criteria: waist circumference greater than 102 cm in men or greater than 88 cm in women; triglyceride concentration 150 mg/dL or higher; high-density lipoprotein cholesterol concentration less than 40 mg/dL in men or less than 50 mg/dL in women; blood pressure greater than 130/greater than 85 mm Hg; and FPG concentration 100 mg/dL or higher.

Patients were excluded if they were diabetic (FPG concentration greater than 126 mg/dL; 2-hour plasma glucose concentration greater than 200 mg/dL). Other exclusion criteria included self-reported hospitalization for treatment of cardiovascular disease 6 months before enrollment, serum creatinine concentration greater than 2.0 mg/dL at baseline, self-reported pancreatitis, recent or significant abdominal surgery, pregnancy and/or intention to

become pregnant during the study, polycystic ovarian syndrome or irregular menses, or use of chromium supplements less than 1 month before screening.

Patients were excluded if they were taking drugs thought to affect glucose metabolism and/ or endothelial function (glucocorticoids, antineoplastic agents, psychoactive agents, and bronchodilators). Patients taking antihypertensive drugs and lipid-lowering agents were allowed to participate provided that dosages were stable for 3 months before enrollment.

Ethical and Safety Considerations

The study protocol and consent form were approved by the Griffin Hospital (Derby, Connecticut) Institutional Review Board and the Yale University (New Haven, Connecticut) Human Investigation Committee and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained, and all participants received a total of $475 (divided among assessment visits) as compensation for their participation. For safety monitoring, unblinded subject treatment assignment was maintained by a data and safety monitoring board.

Study Design and Interventions

This study was a randomized, double-blind, placebo controlled, modified cross-over clinical trial to investigate the effects of daily chromium supplementation for 6 months at 2 dosage levels (500 mcg and 1000 mcg of chromium picolinate daily) on serum measures of insulin sensitivity and glucose tolerance in adults with IGT, IFG, and metabolic syndrome.

The study used a modified cross-over (Latin square) design encompassing both paired (cross-over) and unpaired comparisons with statistical methods and sample size tailored to serve both purposes (see Statistical Analysis).

The study was designed and powered to compare the 6-month effects of 500 mcg to 1000 mcg of chromium on insulin resistance (homeostasis model assessment of insulin resistance [HOMA-IR]), which provided adequate power (see Statistical Analysis) to detect a change in 2-hour plasma glucose and endothelial function. Effects of chromium at each dosage were compared with placebo as a paired (cross-over) comparison after 6 months of use. Because the time required for chromium to wash out fully is unknown, a posttreatment phase of 6 months was incorporated into the design following 12 months of intervention and placebo (Fig. 1).

Patients meeting eligibility criteria were randomly assigned to 500 mcg daily or 1000 mcg daily of chromium picolinate and then further randomized to chromium/placebo or placebo/ chromium sequences. After completing the initial 6-month period, participants immediately crossed over to the alternate assignment (Fig. 1). All investigators and participants were blinded to treatment assignment.

The 2 dosages of chromium picolinate (500 mcg or 1000 mcg daily) and placebo capsules came in the form of capsules similar in shape, size, and appearance, donated by Nutrition 21, Inc (Purchase, New York). Placebo capsules were indistinguishable from those containing chromium. Supplying pharmacy personnel encoded the treatment supplements and matching placebos.

Outcome Measures

The primary outcome measures were serum insulin, HOMA-IR, 2-hour plasma glucose, fasting plasma glucose, and 2-hour insulin during oral glucose tolerance testing assessed after 6 months of chromium use. Insulin resistance was calculated with the HOMA-IR by

using the following equation: HOMA-IR = fasting plasma insulin (µIU/mL) × FPG (mmol/L) × 22.5 (13).

Secondary outcome measures included weight, waist circumference, body mass index (BMI), blood pressure, endothelial function as assessed by flow-mediated dilatation (FMD) of the brachial artery, blood glycohemoglobin, total serum cholesterol, serum high-density lipoprotein cholesterol, serum low-density lipoprotein cholesterol, serum triglycerides, and urinary microalbumin-to-creatinine ratio.

Participants were weighed after removing their heavy outer garments and shoes, standing on a calibrated scale, standing in the center of the platform with weight distributed evenly to both feet. Waist circumference was measured at the level of the umbilicus in a horizontal position. BMI was calculated at each visit. Blood pressure was determined using the Datascope Accutorr Plus automatic digital blood pressure device with the participant supine.

Our endothelial function assessment methods have been previously reported (14). In brief, endothelial function as FMD was measured noninvasively in the right brachial artery with high-frequency ultrasonography (Sonos 4500; Phillips Medical Systems, Andover, Massachusetts) in accordance with published guidelines (15). Measures of vessel diameter and flow velocity were obtained by a single dedicated vascular clinical research specialist blinded to subject treatment status. To account for potential variability in stimulus strength, FMD was divided by flow at 15 seconds after cuff deflation to create a stimulus-adjusted response measure. Endothelial function was assessed in the fasting state, with a nitroglycerin control, and at 90 minutes post-OGTT to assess the change in FMD between fasting and fed states. (A glucose load has been associated with transient endothelial dysfunction in healthy, prediabetic, and diabetic populations [16–19]; nutritional interventions [14,20,21] have been shown to mitigate acute [immediate] endothelial dysfunction.)

Laboratory measures including FPG, 2-hour plasma glucose, glycohemoglobin, lipid panel, and urinary markers were collected and analyzed at Griffin Hospital (Derby, Connecticut) using standard procedures at each visit. Insulin concentrations were measured at the Yale Center for Clinical Investigation Core Laboratory (New Haven, Connecticut).

Statistical Analysis

A sample size of 60 participants, allowing for 20% attrition and nonadherence, was predicted to provide 90% power (8) to detect a minimal difference of 9.5% in HOMA sensitivity between the 500-mcg and 1000-mcg arms ($\alpha = 0.05$). A standard deviation of 10.1 was used on the basis of previous literature (22). This sample size also provided greater than 80% power to detect a change of 15% in 2-hour plasma glucose concentration and 0.5% in FMD between the 500-mcg and 1000-mcg groups at 6 months.

Analysis was by intention-to-treat; 6-month postintervention analysis was conducted on those having completed 6-month assessments (primary end point) in the cross-over design. Missing individual data were addressed by the last observation carried forward method.

Statistical analysis was conducted using SAS software (Version 9.1, SAS Institute, Cary, North Carolina). Independent samples *t* tests, chi-square tests, and Mann-Whitney tests were used to compare participants at baseline. Descriptive and exploratory analyses of all measured outcomes were performed before embarking on modeling or hypothesis testing procedures. Normally distributed data were analyzed using repeated measures analysis of variance to assess differences in intraindividual responses across treatments for all outcome measures, while non-normally distributed data were analyzed using the Mann-Whitney test. Assessment of treatment effects between dosage groups, where baseline between-group

differences were observed to be either statistically significant (*P*<.05) or approaching trend-level significance (*P*<.10), was conducted using analysis of covariance, with baseline values entered into the model to control for those differences. The combined effect of independent variables (age, sex, BMI at baseline, metabolic syndrome, and treatment sequence) and treatment assignment on all outcome measures was assessed with multivariable models.

To assess the effect of different treatment assignments on outcome measures, we computed 95% confidence intervals (CI) for mean changes from baseline following each treatment assignment. Comparisons across treatment assignments were made using the 95% CI around the mean change of outcome measures from their baseline values. When the 95% CI of mean change of one treatment assignment was not included within the 95% CI of mean change of another treatment assignment (ie, nonoverlap), we considered the 2 treatment assignments significantly different at *P*<.05. Mean change from baseline values of outcome measures after each treatment assignment was considered significant when the 95% CI around the mean change did not include zero.

RESULTS

Of the 243 persons screened for eligibility, 80 did not meet eligibility criteria, 47 refused to participate, and 56 were not randomized for other reasons (Fig. 1). Sixty participants were ultimately randomly assigned to 500-mcg (n = 30) or 1000-mcg (n = 30) sequences. One participant in the 1000-mcg sequence withdrew consent after randomization because of time commitment. Of the 59 participants enrolled, 56 completed 6-month assessments (primary end point) and 50 participants completed the 6-month postintervention assessment (Fig. 1). Spot checks of pill counts were done to assess regimen adherence; 92% of our sample consumed more than 80% of assigned capsules.

Participants ranged in age from 31 to 88 years; the mean (± standard deviation) age of the participants was 56.9 (±12.1) years; and 38 (64%) were women. Additional demographic data are provided in Table 1. At baseline, 18 participants (64%) in the 500-mcg arm and 20 participants (74%) in the 1000-mcg arm were insulin resistant by HOMA-IR (>3.0) (13) (*P* = .43). Furthermore, 14 participants (47%) in the 500-mcg arm and 19 participants (66%) in the 1000-mcg arm had metabolic syndrome by National Cholesterol Education Panel Adult Treatment Panel III criteria (12) (*P* = .19).

Primary Outcomes

No changes were observed in FPG, 2-hour plasma glucose levels, fasting or 2-hour post–oral glucose tolerance test insulin levels, or HOMA-IR as compared with placebo after 6 months of chromium use in either the 500-mcg and 1000-mcg arms (Table 2).

Secondary Outcomes

Six months of chromium supplementation (500 mcg or 1000 mcg) was not associated with any significant changes in glycohemoglobin, weight, waist circumference, BMI, blood pressure, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, or urine microalbumin compared with placebo. A modest change in endothelial function at 6 months was noted in comparing the 500-mcg arm with the 1000-mcg arm; endothelial function improved in the former group (+0.9% [−0.5 to 2.4] vs −1.6% [−3.0 to −0.2] in the latter group at 2-hour post–oral glucose tolerance test) and is of uncertain significance, given the lack of other changes in this parameter across groups (Table 2) and the inverse dose-response. There were no other significant changes observed at the 6-month postintervention assessment on all remaining outcome measures (Table 3).

No significant changes were observed in any of the primary or secondary outcome measures after controlling for age, sex, BMI at baseline, metabolic syndrome, treatment sequence, and treatment assignment.

Four participants developed type 2 diabetes during the course of the study (FPG >126 mg/dL or 2-hour plasma glucose >200 mg/dL). All 4 diabetic participants were in the 500-mcg arm, although at the time of diagnosis, 2 were in the placebo-first sequence while 2 were in the chromium-first sequence. No serious adverse events were reported.

DISCUSSION

In this randomized prospective study involving adult patients at risk for diabetes, chromium supplementation, at 2 dosing levels, had no substantive effect on any direct measure of glucose metabolism or indirect measures of insulin action. Chromium therefore appears to be ineffective on markers thought to be related to the development of type 2 diabetes in these high-risk patients. No differences were seen after 6 months of active treatment vs placebo or after 6-month postintervention assessment. The single significant improvement in endothelial function between participants in the 500-mcg arm compared with participants in the 1000-mcg arm is probably a statistical artifact or random finding due to multiple comparisons, inconsistency with a dose-response effect, and lack of corroboration seen in the stimulus-adjusted response measure. In previous work, including our own (14,20,23,24), we detected a significant improvement in endothelial function (as FMD) with a "cardiac risk modification" strategy (25). One proposed explanation is that endothelial function may aggregate the effect of numerous biomarkers of circulatory health. Accordingly, the impact of a single intervention may be amplified when endothelial function is measured. Thus, a positive effect of chromium on endothelial function might have suggested a benefit too subtle to capture with our relatively more crude metabolic measures. However, the absence of any such effect buttresses our conclusion that chromium was without substantial benefit in this population.

Our results are congruent with findings from a recent study performed in our laboratory showing no effect of 1000 mcg of chromium picolinate on weight loss and adiposity in 80 overweight individuals (26). Other recent trials have found similar results. In a randomized trial of 63 persons with metabolic syndrome, Iqbal et al found no effect of 1000 mcg of chromium picolinate on insulin sensitivity, glucose metabolism, body weight, serum lipids, or measures of inflammation and oxidative stress (27). Gunton et al found no changes in 1- and 2-hour glucose tolerance, FPG, fasting insulin, HOMA-IR, and lipid measures in a 3-month randomized controlled trial using 800 mcg of chromium in 40 patients with IGT (28). Earlier studies had shown positive effects of chromium, but these involved smaller numbers of subjects (7) and shorter treatment durations (8). Other previous studies suggested that the primary factor for a clinical response to chromium supplementation is insulin resistance (29–31). In subjects with type 2 diabetes using sulfonylurea agents, Martin et al (30) demonstrated that chromium picolinate improves insulin sensitivity, improves glucose control, and attenuates body weight and visceral fat compared with placebo. The discrepancy between our results and those of Martin et al may possibly be explained by differences in the study populations, with ours not including patients with diabetes, or by the differential measures of insulin sensitivity used in the 2 studies. HOMA-IR is predominately affected by hepatic sensitivity, while the hyperinsulinemic euglycemic clamp technique used by Martin et al predominately assesses peripheral insulin sensitivity. Wang et al found that baseline insulin sensitivity, as measured by clamp, accounted for nearly 40% of the variance in the clinical response to chromium (31). Patients who were insulin resistant responded to chromium supplementation to a greater degree than those who were not insulin resistant (31).

Strengths of our study include use of 2 doses commonly prescribed in clinical practice and multiple outcome measures. Our study also incorporated a rigorous crossover design where participants served as their own control, reducing variability in the results. A major limitation of the study is a lack of a biomarker assessing serum chromium levels at baseline and during therapy. Although current evidence suggests that chromium deficiency in humans are rare, it is possible that chromium-deficient populations may respond to chromium supplementation. Other limitations include relatively broad inclusion criteria. IFG and IGT, especially when those abnormalities are found in isolation (ie, IFG alone or IGT alone), may represent different pathophysiologic derangements and differential risks for developing future diabetes (32). Although participants in our study were largely insulin resistant with a baseline mean HOMA-IR of 4.2, it is conceivable that a greater degree of insulin resistance may be required to detect a robust response to chromium. It is also possible that HOMA-IR, which as mentioned, is largely influenced by hepatic insulin sensitivity (32), is not refined enough as a marker to exhibit an insulin-sensitizing effect of chromium. Despite these concerns, if chromium had any beneficial response on glucose metabolism in participants in our study, improvement in some of the parameters we measured would be expected. We note, for example, that our postchallenge insulin levels (post–oral glucose tolerance testing), which reflect both hepatic and peripheral insulin sensitivity (33), were unchanged compared with those of the placebo group.

CONCLUSION

Chromium supplementation does not appear to ameliorate insulin resistance or impaired glucose metabolism, and thus is unlikely to attenuate diabetes risk. Endocrinologists should therefore not endorse this therapy as part of a diabetes prevention strategy.

Abbreviations

BMI	body mass index
CI	confidence interval
FMD	flow-mediated dilatation
FPG	fasting plasma glucose
HOMA-IR	homeostasis model assessment of insulin resistance
IFG	impaired fasting glucose
IGT	impaired glucose tolerance

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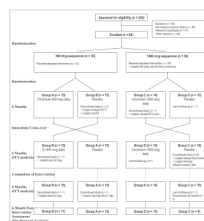
Fig. 1.
Study Design and Flow Diagram.

Table 1

Baseline Characteristics of Patients in the 500-mcg and 1000-mcg Arms[a]

Variable	Groups A and B 500 mcg (n = 30)	Groups C and D 1000 mcg (n = 29)	P value
Sex, No. (%)			
Male	11 (37)	10 (34)	>.99
Age, y	54.7 (10.6)	59.3 (13.3)	.15
Anthropometric Measures			
Weight, lb	90.5 (13.8)	91.4 (22.9)	.84
Waist circumference, cm	107.2 (7.9)	110.4 (15.8)	.41
Body mass index, kg/m^2	33.4 (6.1)	32.7 (5.6)	.64
Metabolic syndrome[b]			
Yes, No. (%)	14 (46.7)	19 (65.5)	.19
Blood pressure			
Systolic, mm Hg	129.3 (12.3)	129.6 (14.4)	.93
Diastolic, mm Hg	75.6 (10.7)	73.4 (12.5)	.79
Laboratory values			
Fasting plasma insulin, μIU/mL	15.6 (8.1)	18.2 (11.6)	.33
2-Hour OGTT insulin, μIU/mL[c]	61.0 (18, 226)	77.5 (14, 483)	.32
Fasting plasma glucose, mg/dL	103.8 (10.8)	98.9 (9.0)	.06
2-hour OGTT glucose, mg/dL	131.8 (41.9)	125.8 (30.0)	.53
HOMA-IR[d]	4.0 (2.0)	4.4 (2.7)	.54
Whole blood hemoglobin A$_{1c}$, %	5.7 (0.4)	5.7 (0.5)	.90
Serum total cholesterol, mg/dL	187.8 (26.5)	185.0 (36.4)	.73
Serum HDL cholesterol, mg/dL	51.7 (11.6)	45.0 (11.6)	.03
Serum LDL cholesterol, mg/dL	112.0 (26.5)	116.2 (29.2)	.56
Serum triglycerides, mg/dL	120.1 (49.3)	120.5 (48.2)	.98
Urine microalbumin[c]	5.6 (0.0, 90.1)	7.1 (0.0, 57.8)	.24
Serum creatinine, mg/dL	0.9 (0.2)	0.9 (0.2)	.53
Endothelial function			
FMD pre OGTT, % Δ	7.8 (3.9)	9.5 (4.7)	.15
FMD pre OGTT nitro, % Δ	15.3 (5.7)	16.2 (5.9)	.56
FMD post OGTT, % Δ	9.5 (4.5)	10.2 (5.0)	.56
SARM pre OGTT	0.1 (0.1)	0.1 (0.1)	.50
SARM post OGTT	0.1 (0.1)	0.1 (0.1)	.42

Abbreviations: FMD, flow-mediated dilatation; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; SARM, stimulus-adjusted response measure.

[a] Data are expressed as mean (standard deviation) unless otherwise noted.

[b] Metabolic syndrome as defined by National Cholesterol Education Program Adult Treatment Panel III criteria.

[c] Values for 2-hour OCTT and microalbumin are expressed as median (minimum, maximum).

[d] HOMA-IR by using the mathematical approximation: HOMA-IR = fasting plasma insulin (µIU/mL) × fasting plasma glucose (mmol/L) × 22.5.

Table 2

Changes From Baseline Values in 500-mcg and 1000-mcg Arms After 6 Months[a]

Variable	Group A and B		Group C and D	
	500 mcg (n = 30)	Placebo (n = 30)	1000 mcg (n = 29)	Placebo (n = 29)
Anthropometric measures				
Weight, lb	−0.1 (−3.1 to 2.8)	−1.4 (−4.3 to 1.6)	2.6 (−0.5 to 5.7)	0.4 (−2.7 to 3.5)
Waist circumference, cm	−0.1 (−2.1 to 1.9)	0.9 (−1.1 to 2.9)	0.1 (−2.7 to 2.8)	1.6 (−1.2 to 4.3)
Body mass index, kg/m²	−0.1 (−0.6 to 0.5)	−0.3 (−0.8 to 0.2)	0.4 (−0.1 to 0.9)	−0.0 (−0.6 to 0.5)
Blood pressure				
Systolic, mm Hg	1.3 (−3.3 to 5.8)	−1.2 (−5.7 to 3.3)	1.3 (−3.2 to 5.7)	4.6 (0.2 to 9.0)
Diastolic, mm Hg	2.8 (−0.6 to 6.1)	3.4 (−0.1 to 6.8)	0.1 (−3.0 to 3.3)	1.6 (−1.6 to 4.7)
Laboratory values				
Fasting plasma insulin, μIU/mL	1.3 (−1.0 to 3.5)	−1.0 (−3.2 to 1.2)	0.7 (−1.6 to 3.0)	−0.4 (−2.7 to 1.9)
2-Hour OGTT insulin, μIU/mL	−1.0 (−11.6 to 9.6)	−7.4 (−18.0 to 3.1)	6.3 (−28.5 to 41.2)	5.1 (−29.7 to 39.9)
Fasting plasma glucose, mg/dL	−1.0 (−3.9 to 1.9)	−2.8 (−5.7 to 0.1)	−0.3 (−3.8 to 3.1)	−0.5 (−3.9 to 3.0)
2-hour OGTT glucose, mg/dL	0.8 (−13.2 to 14.1)	−0.1 (−14.1 to 13.9)	−2.9 (−15.0 to 9.2)	5.7 (−6.4 to 17.8)
HOMA-IR[b]	0.3 (−0.4 to 1.1)	−0.4 (−1.1 to 0.4)	0.2 (−0.4 to 0.8)	−0.1 (−0.7 to 0.5)
HOMA-IR[b], % Δ	7.1 (−6.7 to 21.0)	−6.9 (−20.8 to 6.9)	5.8 (−8.8 to 20.2)	7.1 (−7.5 to 21.6)
Whole blood hemoglobin A_{1c}, %	0.1 (0.0 to 0.2)	0.1 (0.0 to 0.2)	0.0 (−0.1 to 0.1)	0.1 (−0.0 to 0.2)
Serum total cholesterol, mg/dL	−2.9 (−11.0 to 5.1)	−6.8 (−14.9 to 1.2)	−3.1 (−12.5 to 6.3)	2.4 (−7.0 to 11.8)
Serum HDL cholesterol, mg/dL	1.9 (−0.1 to 4.0)	0.6 (−1.4 to 2.6)	3.1 (−2.6 to 8.9)	0.3 (−5.4 to 6.0)
Serum LDL cholesterol, mg/dL	−6.4 (−13.2 to 0.4)	−7.1 (−13.9 to −0.3)	−5.9 (−14.6 to 2.8)	0.03 (−8.7 to 8.8)
Serum triglycerides, mg/dL	8.7 (−7.5 to 24.9)	−0.9 (−17.1 to 15.4)	−2.9 (−17.1 to 11.2)	10.4 (−3.8 to 24.5)
Urine microalbumin	−1.4 (−3.9 to 1.2)	−2.5 (−5.1 to 0.1)	1.2 (−2.8 to 5.2)	1.6 (−2.4 to 5.6)
Serum creatinine, mg/dL	0.1 (−0.0 to 0.0)	0.0 (−0.0 to 0.0)	0.0 (−0.0 to 0.0)	0.0 (−0.0 to −0.0)
Endothelial function				
FMD pre OGTT, % Δ	1.0 (−0.2 to 2.3)	1.0 (−0.3 to 2.7)	−0.1 (−1.1 to 1.4)	−0.2 (−1.1 to 1.5)
FMD pre OGTT nitro, % Δ	1.2 (−1.0 to 3.5)	0.1 (−2.1 to 2.4)	0.1 (−1.8 to 1.9)	−0.7 (−1.1 to 2.6)
FMD post OGTT, % Δ	0.9 (−0.5 to 2.4)	0.1 (−1.3 to 1.6)	−1.6 (−3.0 to −0.2)	−0.4 (−1.8 to 1.0)
SARM Pre OGTT	0.0 (−0.0 to 0.0)	0.0 (−0.0 to 0.0)	0.0 (−0.0 to 0.0)	0.0 (−0.0 to 0.0)
SARM Post OGTT	−0.0 (−0.1 to 0.1)	0.0 (−0.0 to 0.1)	0.0 (−0.0 to 0.0)	0.0 (−0.0 to 0.0)

Abbreviations: FMD, flow-mediated dilatation; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; SARM, stimulus-adjusted response measure.

[a]Data are expressed as mean change (95% confidence interval).

[b]HOMA-IR by using the mathematical approximation: HOMA-IR = fasting plasma insulin μIU/mL × fasting plasma glucose (mmol/L) × 22.5.

Table 3

Changes From Baseline Values in 500-mcg (Group A) and 1000-mcg (Group C) Arms at 6 Months Postintervention[a,b]

Variable	Group A 500 mcg (n = 12)	Placebo (n = 10)	Group C 1000 mcg (n = 10)	Placebo (n = 10)
Anthropometric measures				
Weight, lb	−1.1 (−7.7 to 1.8)	−2.1 (−8.4 to 4.3)	−2.7 (−7.2 to 1.8)	−2.5 (−7.0 to 2.0)
Body mass index, kg/m^2	−0.2 (−1.4 to 1.0)	−0.4 (−1.5 to 0.8)	−0.4 (−1.1 to 0.3)	−0.4 (−1.1 to 0.3)
Blood pressure				
Systolic, mm Hg	−0.1 (−6.8 to 5.0)	−1.7 (−7.4 to 3.9)	−6.8 (−15.3 to 1.7)	3.8 (−4.7 to 12.3)
Diastolic, mm Hg	4.6 (−0.2 to 9.4)	6.0 (1.6 to 10.4)	−0.8 (6.9 to 5.3)	1.8 (−4.3 to 7.9)
Laboratory values				
Fasting plasma insulin, μIU/mL	−4.2 (−8.1 to 0.3)	−1.3 (−5.0 to 2.4)	−0.2 (−5.4 to 5.0)	−1.2 (−6.4 to 4.0)
2-Hour OGTT insulin, μIU/mL	−7.5 (−32.9 to 18.0)	−10.6 (−36.1 to 14.8)	−13.6 (−87.8 to 60.6)	−0.5 (−74.7 to 73.6)
Fasting plasma glucose, mg/dL	−7.4 (−14.6 to 0.3)	−3.8 (−10.0 to 2.4)	−1.7 (−10.9 to 7.5)	0.3 (−8.9 to 9.5)
2-hour OGTT glucose, mg/dL	−18.0 (−39.3 to 3.3)	−10.3 (−28.7 to 8.2)	−2.7 (−26.5 to 21.10)	−2.8 (−26.6 to 21.0)
HOMA-IR[c]	−1.5 (−2.9 to −0.0)	−0.5 (−1.8 to 0.7)	−0.2 (−1.7 to 1.3)	−0.3 (−1.8 to 0.7)
HOMA-IR[c], % Δ	−22.6 (−50.2 to 5.1)	−8.6 (−32.2 to 14.9)	11.5 (−26.3 to 49.4)	5.3 (−32.6 to 43.2)
Whole blood hemoglobin A$_{1c}$, %	0.2 (−0.0 to 0.4)	0.1 (−0.1 to 0.3)	0.1 (−0.2 to 0.5)	0.3 (−0.0 to 0.6)
Serum total cholesterol, mg/dL	13.1 (−7.5 to 33.7)	−4.5 (−23.3 to 14.3)	−8.8 (−23.7 to 6.1)	−7.2 (−22.1 to 7.7)
Serum HDL cholesterol, mg/dL	5.8 (−1.8 to 9.8)	1.7 (−2.0 to 5.3)	0.9 (−2.7 to 4.5)	2.3 (−1.2 to 5.9)
Serum LDL cholesterol, mg/dL	3.1 (−14.0 to 20.2)	−7.2 (−22.8 to 8.5)	−11.9 (−27.4 to 3.6)	−10.3 (−25.8 to 5.2)
Serum triglycerides, mg/dL	22.7 (−18.0 to 63.4)	11.6 (−25.5 to 48.7)	9.1 (−6.2 to 24.4)	5.0 (−10.3 to 20.3)
Urine microalbumin	3.1 (−7.4 to 13.5)	−6.6 (−17.1 to 3.8)	−3.5 (−10.6 to 3.5)	0.6 (−6.4 to 7.7)
Serum creatinine, mg/dL	−0.0 (−0.1 to 0.0)	−0.0 (−0.1 to 0.0)	−0.0 (−0.1 to 0.1)	0.1 (−0.0 to 0.2)
Endothelial function				
FMD pre OGTT, % Δ	1.9 (−0.6 to 4.3)	1.5 (−0.9 to 3.9)	1.6 (−0.7 to 3.8)	0.8 (−1.5 to 3.0)
FMD pre OGTT nitro, % Δ	3.7 (−1.9 to 9.2)	−0.0 (−5.1 to 5.0)	−2.8 (−6.5 to 1.0)	−0.2 (−3.7 to 3.4)
FMD post OGTT, % Δ	−0.4 (−3.8 to 2.9)	0.1 (−3.2 to 3.4)	0.5 (−2.5 to 3.6)	−0.4 (−3.7 to 2.8)
SARM pre OGTT	−0.0 (−0.1 to 0.1)	0.0 (−0.1 to 0.1)	0.0 (−0.0 to 0.1)	0.0 (−0.0 to 0.1)
SARM post OCTT	−0.1 (−0.2 to 0.1)	0.1 (−0.1 to 0.2)	0.0 (−0.0 to 0.1)	0.0 (−0.0 to 0.1)

Abbreviations: FMD, flow-mediated dilatation; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; SARM, stimulus-adjusted response measure.

[a] Data are expressed as mean change (95% confidence interval).

[b] By design, the immediate cross-over of groups B and D from placebo to intervention did not allow for 6-month post-placebo data collection (see Fig. 1).

[c] HOMA-IR by using the mathematical approximation: HOMA-IR = fasting plasma insulin (μIU/mL) × fasting plasma glucose (mmol/L) × 22.5.